REMARKS

Applicants have added claims 18-21 to more clearly define the invention. Applicants disclose a method that is a "ditherapy" for treating obesity wherein subjects are treated with just metformin and a particular Markush group of PPARα agonists. The two compounds may be administered in pharmaceutical formulations either sequentially or simultaneously as taught in claims 16 and 17, paragraph [0051] and the Examples. Support for claims 18-21 is found e.g., in claims 16 and 17, paragraph [0051] and the Examples.

Applicants have amended claims 16 and 17 to depend on claim 18.

Applicants have amended claim 12 to recite that the subject in need there of is administered "a pharmaceutical formulation consisting of an effective dosage of a PPARα agonist, ~~and~~ an effective dosage of metformin, and a pharmaceutical carrier, wherein the PPARα agonist is selected from the group consisting of ...." Support for this amendment is found e.g., in paragraph [0016], [0022], and [0042].

Claims 12-13 and 15-17 stand rejected under 35 U.S.C. 102(e) for purportedly being anticipated by Cheng et al. (US2003/0092736). Applicants respectfully disagree.

> Anticipation under 35 U.S.C. §102 requires the disclosure in a single piece of prior art of each and every limitation of a claimed invention.
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> *Electro Med. Sys. S.A. v. Cooper Life Sciences*, 32 USPQ2d 1017, 1019 (Fed. Cir. 1994).

Applicants' claimed methods for treating obesity is a ditherapy wherein a subject in need thereof is administered a pharmaceutical formulation consisting of a pharmaceutical carrier and an effective dosage of particular PPARα agonists and an effective dosage of metformin, wherein the PPARα agonist is selected from a particular Markush group. In contrast, Cheng *et al.* paragraph [0493],

cited by the Examiner, teaches the administration of their new azole acid derivatives, alone or in combination with antidabetic and/or antilipidemic agents and other therapeutic agents. Cheng et al. discloses that the new azole acid derivatives modulate blood glucose levels, triglyceride levels, insulin levels and non-esterified fatty acid levels, and to method for treating diabetes, as well as hyperglycemia, hyperinsulinemia, hyperlipidemia, obesity, atherosclerosis and related diseases employing these new azole acid derivatives. In addition, Cheng *et al.* discloses lists of many possible combinations of many agents to treat many different diseases, from diabetes to cancers (see e.g. claims 16-19), and contains numerous paragraphs disclosing lists of therapeutic agents that could be used (see e.g., claim 14), always in association with the new azole acid derivatives of the invention. A general disclosure of various compounds always in combination with Cheng's azole acid derivatives does not anticipate the use of the particular combinations recited in Applicants' claims or the synergistic effect of metformin in combination with the fibrates recited in claim 13 (see Table 3) to treat a specific disease *(viz* obesity).

Cheng *et al.* fails to teach, or suggest, Applicants' ditherapy, a method for treating obesity by treating a patient with a pharmaceutical composition consisting of metformin and the particular PPARα agonists recited in Applicants' claims. As such, Cheng et al. fails to disclose each and every limitation of a claimed invention and fails to anticipate Applicants' invention.

In view of the foregoing remarks and amendments to the claims, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. 102(e).

Claims 12-13 and 15-17 stand rejected under 35 U.S.C 103(a) over Lee et al. (Obesity Research 1998)("Lee") in view of Perry (U.S. 5,942,500)("Perry"). Applicants respectfully disagree. Lee and Perry alone or in combination fail to teach or suggest the claimed method and fail to predict the synergistic effects

produced by a formulation consisting of metformin and fenofibrates on obesity (see Table 3).

Lee discloses a study of the effect of metformin on twelve diet-treated non-insulin-dependent diabetes mellitus women with obesity. It is concluded that metformin treatment leads to a reduction in the weight of these patients, see also the present application, Table 3, disclosing the effect of meformin alone on weight loss. However, as the Examiner acknowledges, Lee does not suggest combining metformin with a PPARα agonist for treating obesity. Perry does not compensate for Lee's deficiencies.

The Examiner acknowledges that Lee does not suggest combining metformin with a PPARα agonist and that Perry does not suggest combining a fibric acid derivative with metformin. Nonetheless, the Examiner contends one of skill in the art would be motivated to use two compounds, which the Examiner contends have been used to aid in weight loss, in order to improve weight loss results. However, neither Lee nor Perry disclose that fibrates have been used to aid in weight loss. In fact, Perry only describes fibrates as previously known anti-lipidic agents which "aid in the breakdown of fats" (Perry Col. 3, lines 40-42). Fibrates are known anti-cholesterolemic agents, being able to lower triglycerides and elevate the level of plasma HDL cholesterol. Thus, Perry is no more than a general disclosure that fibrates are generally well known as anticholesterolemic agents. Such a general disclosure is insufficient motivation for one of skill in the art to combine just the particular PPARα agonist recited in Applicants' claims with metformin, or any other particular compound, to treat obesity, and does not predict the synergistic effect that Applicants have discovered.

In addition, Perry teaches away from using the compounds listed in Col. 3, lines 30-42, which includes fibric acid derivatives such as clofibrate, fenofibrate and gemfibrozil, by concluding "However, the use of drugs often included

undesirable side effects" (Col. 3, lines 43-44) and then focusing his analysis on other compounds.

In particular, Perry's disclosure is focused on a composition comprising a linear aminopolysaccharide having a structure similar to, and including, (1-4)-linked 2-amino-2-deoxy-beta-D-gluco pyranose and a lipoprotein lipase, and optionally an acid. Perry's composition is purported to reduce bad cholesterol, which is the main purpose of the invention. Perry mentions that a second possible benefit of his composition is weight reduction even though a person consumes dietary lipid fats (see column 4, lines 14-17). Perry presents no experimental results demonstrating such an effect. Even if Perry's composition reduced weight gain, Perry teaches that the composition inhibits ingestion of LDL cholesterol while consuming a diet high in lipids produced from meats and other fatty foods (column 5, lines 30-33). Therefore, and as indicated in Perry, column 5, lines 56-59, the composition is to be taken specifically with a diet that includes fatty acids, and is not to be used if one is consuming nonfat foods. Perry thus relates only to avoiding blood lipid accumulation due to a diet having a high lipid content. Perry does not teach or suggest combining his compound with metformin and Perry leads one of skill in the art away from using compounds such as fibric acid derivatives e.g., clofibrate, fenofibrate and gemfibrozil. Thus, Perry would not motivate one of skill in the art to treat obesity with a pharmaceutical composition consisting of a carrier, metfomin, and the particular PPARα agonists recited in Applicants' claims.

Applicants have also disclosed that the combination of metformin with fenofibrate unexpectedly produces synergistic effects, see Table 3. Such synergistic effects are not taught or suggested by either Lee or Perry, nor would one of skill in the art based on Lee or Perry expect such results. As such, the combination of Lee and Perry does not render a method for treating obesity with a pharmaceutical composition consisting of a carrier, metfomin, and the particular PPARα agonists recited in Applicants' claims obvious.

In view of the foregoing remarks and amendments to the claims, Applicants request that the Examiner reconsider and withdraw the rejection of Claims 12-13 and 15-17 under 35 U.S.C 103(a) over Lee in view of Perry.

Claims 12-17 stand rejected under 35 U.S.C. 103(a) for purportedly being unpatentable over Lee in view of Chaput et al. (Biochemical and Biophysical Research Communications 2000)("Chaput"). Applicants respectfully disagree.

The Examiner acknowledges that Lee fails to disclose treating obesity with a PPARα agonist. Chaput does not compensate for Lee's deficiencies. Chaput discloses the effect of fenofibrate and rosiglitazone on lowering serum triglycerides with opposing effects on body weight. Results presented by Chaput page 448 show that rosiglitazone has no significant effect on body weight in db/db mice whereas fenofibrate decreases body weight gain in fatty Zucker rats. But, "[t]he cited art must be considered for all that it teaches, and the Examiner is not permitted to pick and choose from those teachings only so much that would render the claims obvious." *ATD Corp. v. Lydall, Inc.* 48 USPQ2d 1321 (Fed. Cir. 1998). Chaput also teaches against fenofibrate having any effect on weight gain in Sprague Dawley rats.

Chaput page 448, right col., discloses that previous reports teach that fenofibrate does not affect body weight in Sprague Dawley rats. Such conflicting results teach away from using fenofibrate for treating obesity. Thus one of skill in the art would not be motivated to particularly combine fenofibrate, or any of the other particular PPARα agonists recited in Applicants' claims, with metformin. Furthermore, one of skill in the art in view of Lee in combination with Chaput would have no reason to expect that fenofibrate in combination with metformin would have a synergistic effect on weight loss. As such, Lee in combination with Chaput does not render the claimed invention obvious.

In view of the foregoing remarks and amendments to the claims, Applicants request that the Examiner reconsider and withdraw the rejection of

Claims 12-17 under 35 U.S.C. 103(a) for purportedly being unpatentable over Lee in view of Chaput.

Claims 12-17 stand rejected under 35 U.S.C. 103(a) for purportedly being unpatentable over Lee in view of Piomelli et al. (US2005/010542)("Piomelli").

The Examiner acknowledges that Lee fails to disclose treating obesity with a PPARα agonist. As discussed below, Piomelli does not compensate for Lee's deficiencies.

Piomelli is related to pharmaceutical use of a combination of PPARα agonists and a CB1 cannabinoid receptor antagonist to reduce excess or unwanted appetites for consumption of appetizing substances, such as foods, alcohol, and psychoactive substances of abuse. While a method for treating or preventing obesity or overweight by administering a combination providing both a cannabinoid CB1 receptor antagonist and a PPARα agonist is mentioned (see paragraph [0024]) such a disclosure is insufficient to motivate one of skill in the art to combine the particular Markush group of PPARα agonists recited in Applicants' claims with metformin in a method to treat obesity. Metformin is not an antagonist of the cannabinoid CBI receptor, and thus one of skill in the art, would not be motivated to use metformin with Piomelli's assays

Furthermore, Piomelli simply provides a laundry list of compounds including, among others, clofibrate, fenofibrate, bezafibrate, gemfibrozil and cipLofibrate, see paragraph [0026]. Paragraph [0026] is included in a long shopping list of compounds that *might* possibly be used, see e.g., paragraph [0025] to [0029], from [0034] to [0041] (OEA, fatty acid alkanolamide compounds and homologue or analog thereof), and in detail from [0145] to [0213]. It is interesting to note that the inventors themselves indicate that clofibrate alone does not inhibit food intake, whereas other PPARα agonists, such as Wy-14643 and GW7647, do (see [0429]). Accordingly, Piomelli's disclosure does not teach or suggest that the fibrates in combination with a cannabinoid CB1 receptor

antagonist are effective in treating or preventing obesity. Thus one of skill in the art based on the teachings of Piomelli, would not be motivated to combine Piomelli with Lee and use metformin in combination with the particular PPARα agonist recited in Applicants' claims.

The foregoing demonstrates that not only would one of skill in the art not be motivated to combine Lee and Piomelli, but also that Lee in combination with Piomelli fails to teach or suggest the invention as claimed. Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 12-17 under 35 U.S.C. 103(a) for purportedly being unpatentable over Lee in view of Piomelli.

Claims 12-17 stand rejected under 35 U.S.C. 103(a) for purportedly being unpatentable over Liu et al. (US2002/0173663)("Liu"). Applicants respectfully disagree for the reasons of record and as discussed below.

Liu provides laundry lists of many compounds and possible combinations of compounds and many diseases that might be treated. Such a disclosure is insufficient to motivate one of skill in the art to combine the particular PPARα agonists with metformin as recited in the claims. And, one of skill in the art would have no reason to expect that their combination would produce the synergistic effect disclosed in Applicants' specification. As such, Liu does not render Applicants' invention obvious and Applicants respectfully request that the Examiner reconsider and withdraw the rejection of Claims 12-17 under 35 U.S.C. 103(a) for purportedly being unpatentable over Liu.

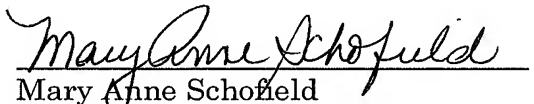
If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and

please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #102717.58257US).

Respectfully submitted,

January 22, 2008



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